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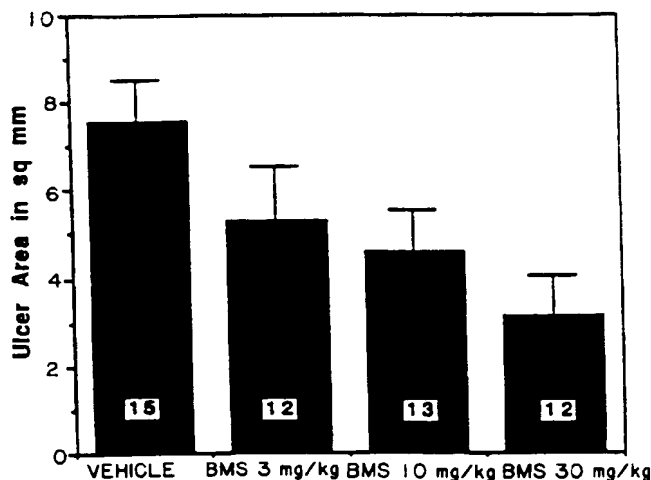
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5d Use of potassium-channel activators for the manufacture of a medicament for the treatment of gastrointestinal ulcers.

(57) Ulcerative conditions of the gastro-intestinal tract, e.g., antiinflammatory-drug-induced ulcers, are treated or prevented by the administration of a potassium channel activator. Methods and combination products are also disclosed for the treatment of inflammatory conditions without causing ulceration of the gastrointestinal tract.



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EP 0 575 749 A2

The present invention relates to a method for protecting against and/or treating ulcerative gastrointestinal conditions, including anti-inflammatory-drug-induced ulcers, employing a potassium channel activator (PCA), as well as to compositions, combinations and improved methods for treating inflammatory conditions.

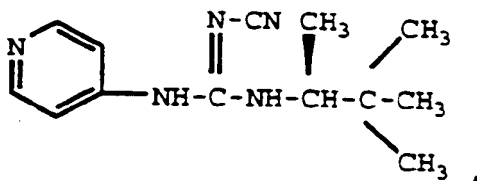
Anti-inflammatory drugs such as aspirin, indomethacin, ibuprofen, meclofenamate, naproxen, phenylbutazone, piroxicam and various corticosteroids are effective in treating or controlling pain, including headache, and in decreasing joint swelling, tenderness, pain and stiffness in conditions such as rheumatoid arthritis. Unfortunately, although much anti-inflammatory drugs are effective in treating pain and inflammatory conditions, they cause development of gastrointestinal ulcers thereby seriously limiting chronic use of these drugs.

In accordance with the present invention, it has now been found that gastrointestinal ulcers are effectively treated using a therapeutic amount of a potassium channel activator (PCA). Additionally, it has been found that the incidence of antiinflammatory drug-induced gastric ulcers is substantially reduced when PCA's are administered with the antiinflammatory drug. Thus, PCA's can be used prophylactically in patients taking antiinflammatory drugs. This can be accomplished by administering a single combination dosage form or by the concomitant administration of a PCA and an antiinflammatory drug. Accordingly, combination products and improved methods of treating inflammation are also provided by the present invention.

Any PCA can be used in the methods and compositions of the present invention. Preferably, PCA's which have little or no vasodilator activity in normal tissue, but which show an anti-ischemic effect in ischemic tissue, are preferred.

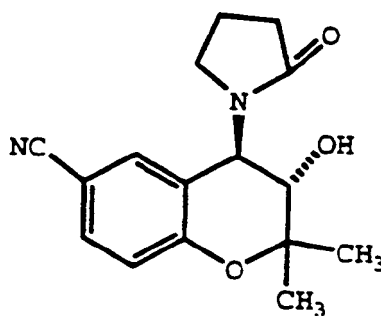
Suitable potassium channel activators include those disclosed in U. S. Patent 4,057,636, especially the compound

A



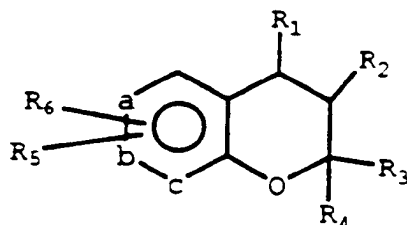
known as pinacidil; those disclosed in European Patent Application 0 274 821, especially the compound

B

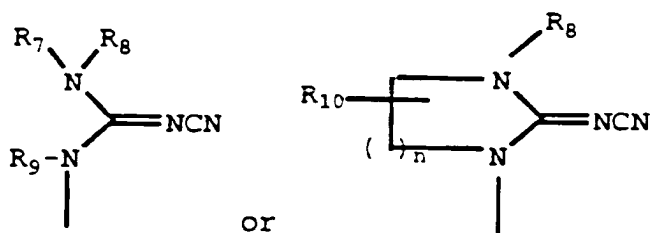


known as cromakalim; nicorandil; minoxidil; compounds in copending application U. S. Ser. No. 661,763 filed February 27, 1991 having the formula

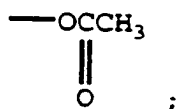
C



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons:
R₁ is

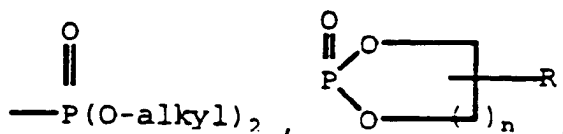


R₂ is hydrogen, hydroxy.



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



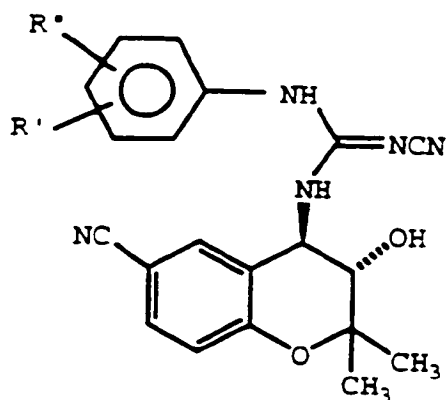
halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCCOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;

R₇ and R₈ are each independently selected from hydrogen, alkyl, alkenyl, aryl (including phenyl substituted with R' and R'' as defined below), (heterocyclo) alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R₇ and R₈ taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R₉ and R₁₀ are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkyl; and
n is 1, 2 or 3;

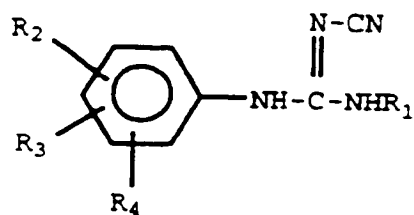
with the compound

C'

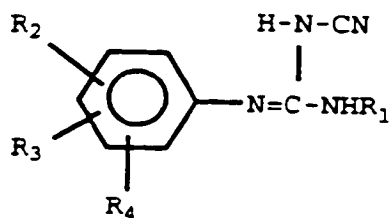
(where R' and R'' are independently hydrogen, cyano, alkyl, alkoxy, nitro, hydroxy, halo, haloalkyl, alkylthio, amino, -N(alkyl)₂, -NHalkyl or benzyloxy with the proviso that at least one of R' and R'' is other than hydrogen)

being preferred;

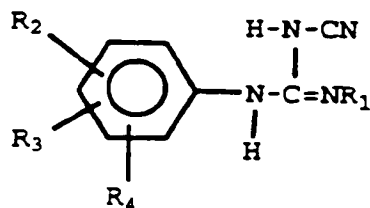
compounds in copending application U. S. Patent 5,011,837 granted April 30, 1991 having the formula

D

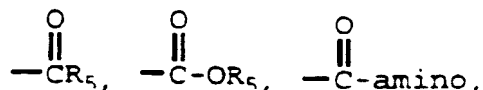
and its possible tautomers

D'

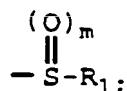
and

D''

wherein R_1 is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;
 R_2 is $-C\equiv N$, $-NO_2$,

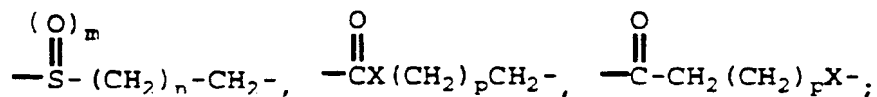


15 CF_3 or



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R_3 and R_4 are each independently selected from $-R_2$, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, $-NHalkyl$, $-N(alkyl)_2$, $-Salkyl$, $-Oarylalkyl$, $-Sarylalkyl$ or $-Saryl$, $-Oaryl$, $-NHarylalkyl$, or R_2 and R_3 taken together are a group which forms a ring with the two carbon atoms to which they are attached,
 25 which group is selected from



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wherein

$m = 1$ or 2 ;

$n = 1-3$;

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$p = 0-2$;

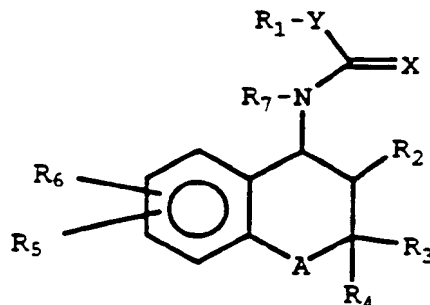
X is O , NR_5 , CH_2 ; and,

R_5 is hydrogen or R_1 ;

compounds disclosed in copending patent application serial number 776,921 filed October 15, 1991 of
 the formula

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E

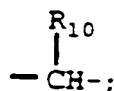


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wherein A can be $-CH_2-$, $-O-$, $-NR_9-$, $-S-$, $-SO-$ or $-SO_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4
 55 carbons;

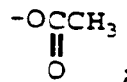
wherein X is oxygen or sulfur;

Y is $-NR_8$, $-O-$, $-S-$ or



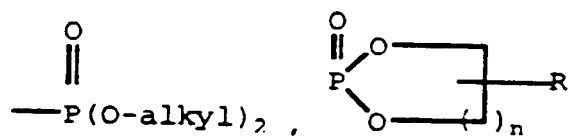
R- is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



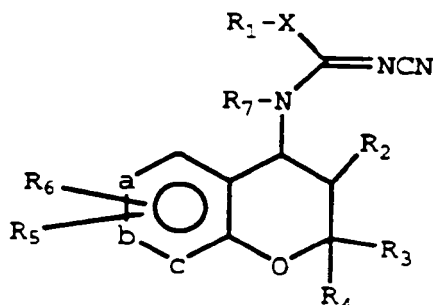
halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , $-\text{OCOalkyl}$, $-\text{OCONRalkyl}$, $-\text{NRCOalkyl}$ and NRCOOalkyl , NRCONR_2 wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;

R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;

n is 1, 2 or 3; and,

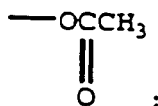
R₁ is hydrogen, hydroxy, alkyl or O-alkyl; and compounds in copending application Serial No. 745,563 filed August 15, 1991 having the general formula



wherein a, b and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;
where X is oxygen or sulfur;

R₁ is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl;

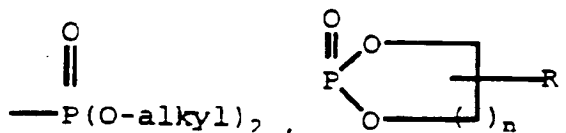
R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl.

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halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NR₂COalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

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R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN and NO_2 ;

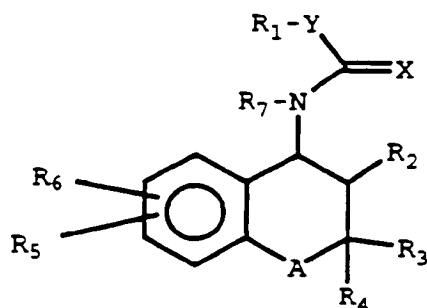
R₇ is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,

n is 1, 2 or 3; and,

compounds disclosed in copending application serial number 630,472 filed December 19, 1990 having the formula

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G



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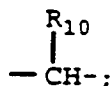
wherein A can be -CH₂-, -O-, -NR₉-, -S-, -SO- or -SO₂-, where R₉ is hydrogen or lower alkyl of 1 to 4 carbons;

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wherein X is oxygen or sulfur;

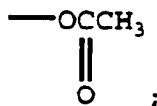
Y is -NR₈, -O-, -S- or

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R₁ is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

45 R_2 is hydrogen, hydroxy,

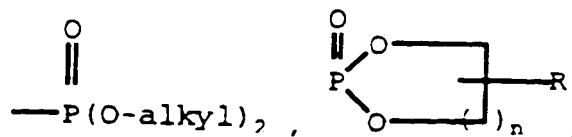


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R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

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R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl or haloalkyl;

R₆ is selected from H, alkyl, halo, OH, o-alkyl, amino and substituted amino, O-alkyl, OCOalkyl, OCONRalkyl, NRCOalkyl and NRCOOalkyl, NRCON(R)₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl or haloalkyl;

R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;

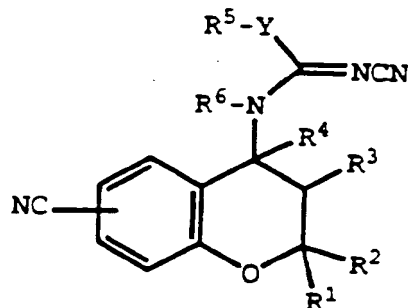
or R₇ and R₈, or R₇ and R₈ taken together can form a 5- to 7-membered saturated or unsaturated ring, which may further include an aryl group fused to 2 carbon atoms of such 5- to 7-membered ring;

n is 1, 2 or 3; and,

R₁₀ is hydrogen, hydroxy, alkyl or O-alkyl.

Also suitable for use herein are compounds as disclosed in U. S. 4,988,723 granted January 29, 1991 having the formula

H



wherein

R¹ and R² are each lower alkyl;

R³ is hydroxy or acyloxy and R⁴ is hydrogen or R³ and R⁴ are linked together to form a bond, and

(i) Y is -S-, -O- or a group of the formula:



wherein R⁷ is hydrogen, acyl or lower alkyl which may have suitable substituent(s), and

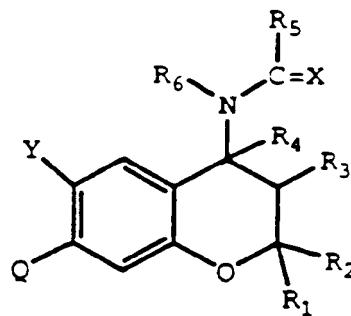
R⁵ and R⁶ are each hydrogen or lower alkyl,

(ii) Y is as defined above, and R⁵ and R⁶ are linked together to form lower alkylene, or

(iii) Y-R⁵ is a heterocyclic group which may have suitable substituent(s), and R⁶ is hydrogen or lower alkyl

compounds as disclosed in EP 214,818 having the formula

J



and salts thereof, wherein

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-5} alkoxy or C_{1-7} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

R_5 is hydrogen, C_{1-6} alkyl optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carbon or amino optionally substituted by one or two independent C_{1-6} alkyl groups, or C_{2-6} alkenyl, amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen, or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-12} carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups and R_6 is hydrogen or C_{1-6} alkyl, or R_5 and R_6 together are $-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2 such that $m + n$ is 1 or 2 and Z is CH_2 , O, S or NR wherein R is hydrogen, C_{1-9} alkyl, C_{2-7} alkanoyl, phenyl C_{1-4} alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen; mono- or bi-cyclicheteroarylcarbonyl;

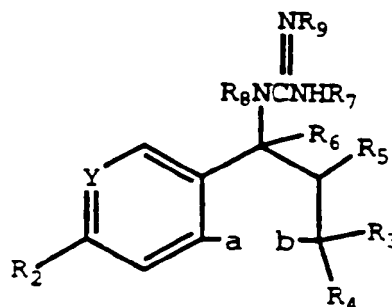
X is oxygen or sulphur;

Y and Q are electron withdrawing groups; and

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy;

compounds as disclosed in EP 359,537 having the formula

K



wherein

a and b together form an -O- or $-CH_2-$ linkage or a bond;

either Y is N and R_2 is hydrogen; or

Y is $C-R_1$;

wherein

either one of R_1 and R_2 is hydrogen and the other is nitro, cyano, halo, CF_3 , formyl, aldoxime, CF_3O , $NO_2-CH=CH-$, $NC-CH=CH-$;

a group R_XX wherein R_X is C_{1-6} alkyl, aryl or heteroaryl either of which may be optionally substituted by one, two or three of C_{1-4} alkyl, C_{1-4} alkoxy, nitro, halo, CF_3 and cyano; and X is $C=O$, $O.C=O$, $C=O.O$.

or a group R_1R_2NZ - wherein R_1 and R_2 are independently hydrogen or C_{1-6} alkyl and Z is $C=O$, SO or SO_2 ; or

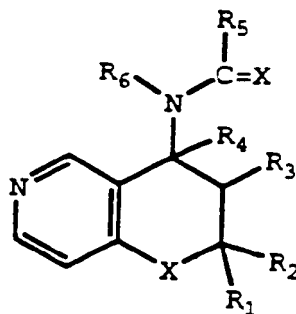
one of R₁ and R₂ is nitro, cyano or C₁₋₃alkylcarbonyl and the other is a different group selected from nitro cyano, halo, C₁₋₃alkylcarbonyl, methoxy or amino optionally substituted by one or two C₁₋₆ alkyl or by C₂₋₇alkanoyl;

either R₅ is hydrogen, hydroxy, C₁₋₆ alkoxy or C₁₋₇ acyloxy; and R₆ is hydrogen; or

either R₇ is hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl; and R₈ is hydrogen or C₁₋₆ alkyl; or

R₉ is CN, NO₂, COR₁₀ wherein R₁₀ is C₁₋₃alkyl, NH₂, NH(C₁₋₃alkyl), CF₃ or phenyl optionally substituted as defined for R₁; and

the $R_8N(NR_9)NHR_7$ moiety is *trans* to the R_5 group when R_5 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy; compounds as disclosed in EP 205,292 having the formula



one of R₁ and R₂ is hydrogen or C₁₋₄alkyl and the other is C₁₋₄alkyl or R₁ and R₂ together are C₂₋₅polymethylene;

R₅ is hydrogen; C₁₋₆ alkyl optionally substituted by up to three halo atoms, by hydroxy, C₁₋₄ alkoxy, C₁₋₆ alkoxy carbonyl, carboxy, or amino optionally substituted by one or two independent C₁₋₆ alkyl groups or disubstituted by C₄₋₅ polymethylene, C₂₋₆ alkenyl; amino optionally substituted by a C₁₋₆ alkyl or C₁₋₆ alkenyl group or by a C₁₋₆ alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen; or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, C₁₋₁₂ carboxylic acyl or amino or aminocarbonyl optionally substituted by one or two C₁₋₆ alkyl groups; or (when X is O). R₅ is selected from the class of carboxy, C₁₋₆ alkoxy carbonyl or aminocarbonyl optionally substituted by one or two C₁₋₆ alkyl groups; and,

R₅ and R₆ together are -CH₂-(CH₂)_n-Z-(CH₂)_m-wherein m and n are 0 to 2 such that m + n is 1 or 2 and Z is CH₂, O, S or NR wherein R is hydrogen, C₁₋₈alkyl C₂₋₇alkanoyl, phenyl, C₁₋₄alkyl, naphthylcarbonyl, phenylcarbonyl or benzyl-carbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C₁₋₆alkyl, C₁₋₆alkoxy or halogen or R is heteroarylcarbonyl;

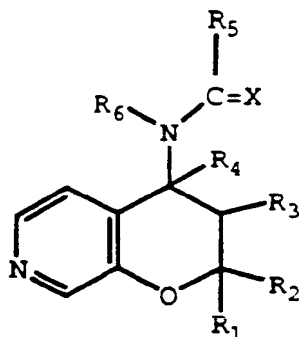
R₅, R₆, X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolinthione optionally substi-

tuted in the phenyl ring as defined for R above;

the nitrogen-containing group in the 4-position being trans to the R₃ group when R₃ is hydroxy, C₁-4 alkoxy or C₁-7 acyloxy;

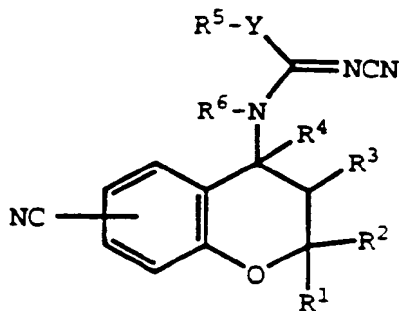
compounds as disclosed in PCT 87/00386 having the formula

M



- and pharmaceutically acceptable salts thereof, wherein R₁ is hydrogen or alkyl; R₂ is alkyl or R₁ and R₂ are polymethylene; R₃ is hydrogen, hydroxy, alkoxy, acyloxy; R₄ is hydrogen or R₃ and R₄ are a bond; R₅ is hydrogen, optionally substituted alkyl, alkenyl, optionally substituted amino, optionally substituted aryl or heteroaryl, carboxy, alkoxy carbonyl or aminocarbonyl; R₆ is hydrogen or alkyl or R₅ and R₆ together are -CH₂-(CH₂)_n-Z-(CH₂)_m-, wherein m and n are 0 to 2, m + n is 1 or 2, Z is CH₂, O, S, NR; R is hydrogen, alkyl, alkanoyl, phenylalkyl, naphthylcarbonyl, phenylcarbonyl, benzylcarbonyl, or heteroaryl-carbonyl; X is O, S or R₅; R₆, X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolinthione; compounds as disclosed in EP 344,747 having the formula

N



wherein

R¹ and R² are each lower alkyl;

R³ is hydroxy or acyloxy and R⁴ is hydrogen; or

R³ and R⁴ are linked together to form a bond, and

(i) Y is -S-, -O- or a group of the formula



wherein

R⁷ is hydrogen, acyl or lower alkyl which may have suitable substituent(s); and

R⁵ and R⁶ are each hydrogen or lower alkyl;

(ii) Y is as defined above; and

R⁵ and R⁶ are linked together to form lower alkylene; or

(iii) Y-R² is a heterocyclic group which may have suitable substituent(s); and

R² is hydrogen or lower alkyl;

and pharmaceutically acceptable salts thereof.

In carrying out the method of the present invention, the PCA may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc., to treat ulcerative gastrointestinal conditions. In methods for treating inflammatory conditions, the PCA's can be administered before, during or after antiinflammatory drug therapy alone or in combination with such drug.

The PCA may be administered systemically, such as orally, parenterally, intranasally or transdermally

The PCA, alone or in combination with an antiinflammatory drug, may be incorporated in a conventional dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

With regard to such systemic formulations, single or divided doses of from about 5 to about 2500 mg, preferably from about 10 to 2000 mg, one to four times daily, may be administered in systemic dosage forms as described above for a period sufficient to reduce existing ulcerative conditions, or may be administered previous to and preferably concurrently with antiinflammatory drugs.

With regard to combinations of the PCA with anti-inflammatory agent, single or divided doses of from 5 to about 2500 mg of PCA, preferably 10 to 2000 mg of PCA, and from about 2 to about 2000 mg anti-inflammatory agent and preferably from about 5 to about 1500 mg anti-inflammatory agent, depending upon the type of anti-inflammatory agent employed, may be administered one to eight times daily.

It will be appreciated that all of the anti-inflammatory drugs disclosed herein are known for treating inflammation and/or pain and may be employed in dosage forms and amounts as disclosed in the Physicians' Desk Reference.

The preferred embodiments of this invention involve using compounds of the general formulae C, E, F or G. Compounds of formula C, E, F or G are useful in the present method where little or no antihypertensive action is desired. Such "selective" compounds are those potassium channel activators which have IC₅₀ (rat aorta) values greater than that of cromakalim. Preferably the IC₅₀ value is 10 times greater and more preferably 100 times greater than that of cromakalim. In other words, the preferred embodiments use compounds which preferably have 1/10 and more preferably 1/100 of the vasorelaxant activity of cromakalim. These include compounds of formula C where R₇ is (or compounds of formula E, F or G where R₇ is) aryl, especially substituted phenyl, arylalkyl, heteroaryl or heteroarylalkyl.

The term "ulcerative conditions of the gastrointestinal tract" as employed herein includes conditions such as gastric ulcers, duodenal ulcers, Crohn's disease, ulcerative colitis, irritable bowel syndrome, and inflammatory bowel disease.

Further, in accordance with the present invention, a new combination is provided which includes a PCA and an anti-inflammatory drug which may be employed in a weight ratio to each other of within the range of from about 0.01:1 to about 100:1, and preferably from about 0.5:1 to about 2:1.

The above combination may be employed to treat pain, joint swelling, and stiffness associated with rheumatoid arthritis or to treat diseases in the manner of known anti-inflammatory agents.

Anti-inflammatory drugs or agents which may be employed herein include, but are not limited to, aspirin, indomethacin, ibuprofen, meclofenamate, naproxen, phenylbutazone, piroxicam, and various corticosteroids including hydrocortisone, dexamethasone, and methylprednisolone.

Example 1

Aspirin-Induced Gastric Erosions

Male Sprague-Dawley rats (150-350 g) were housed separately in cages with wire mesh floors that would allow fecal material to fall through. They were fasted overnight before the experiment and allowed free access to water. On each experiment day, the order of treatments was randomized. One hour after oral dosing with Vehicle (1% methyl cellulose - MO262, Sigma Chemical Co.) or the subject potassium channel activator (3S-trans)-N-(4-chlorophenyl)-N'-cyano-N''-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)guanidine (3, 10 or 30 mg/kg), rats were dosed with aspirin (200 mg/kg, p.o.) prepared in a 1% methyl cellulose vehicle. Three hours after receiving aspirin, each rat was sacrificed by CO₂ asphyxiation. The stomach was removed, slit open along its greater curvature, rinsed with normal saline, and examined under a 2.5X magnifying lens. The gastric erosions were counted and the total area of gastric erosion measured. The results are illustrated in Figure 1 and Table 1 below. The left half of Table 1

summarizes the measured areas of gastric erosion in the four groups of rats: vehicle (mean \pm SEM = 7.57 \pm 0.96 mm²), the subject potassium channel activator (3 mg/kg; 5.31 \pm 1.22 mm²), the subject potassium channel activator (10 mg/kg; 4.58 \pm 0.96 mm²), and the subject potassium channel activator (30 mg/kg; 3.16 \pm 0.89 mm²). The average lesion areas \pm SEM for vehicle and treatment groups are summarized in Figure

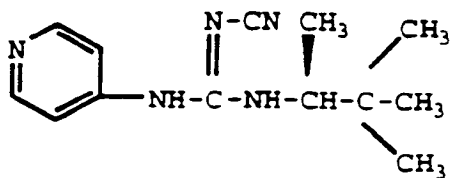
1. The subject potassium channel activator induced reduction in gastric lesion area was statistically significant by analysis of variance ($p = 0.022$). The right half of Table 1 shows the percent protection [i.e., $(7.57 - \text{lesion area})/7.75 \times 100$] afforded by the subject potassium channel activator treatment compared to the average lesion area in the vehicle group. The dose producing a 50% reduction in aspirin-induced gastric lesion area (i.e., ID₅₀) was calculated to be 17.4 mg/kg, p.o. by regression analysis.

55 Claims

RNSDDDD <ED 0575749A2 1 >

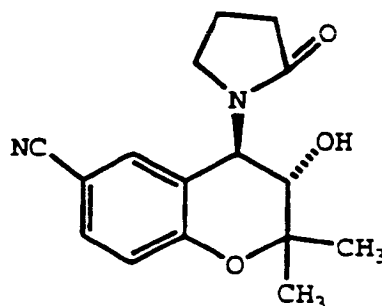
2. The use as defined in claim 1 wherein the potassium channel activator is nicorandil, minoxidil, a compound of the formula

A



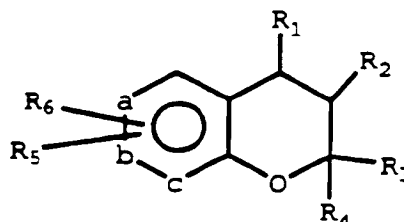
known as pinacidil;

B



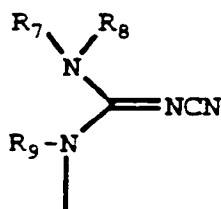
known as cromakalim;

C

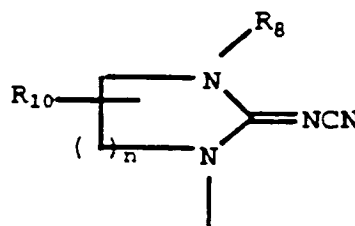


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R₁ is

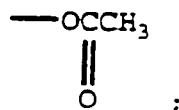


or



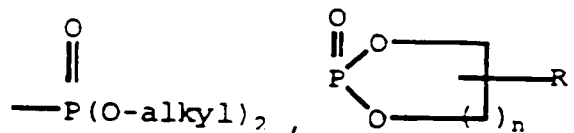
;

R₂ is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



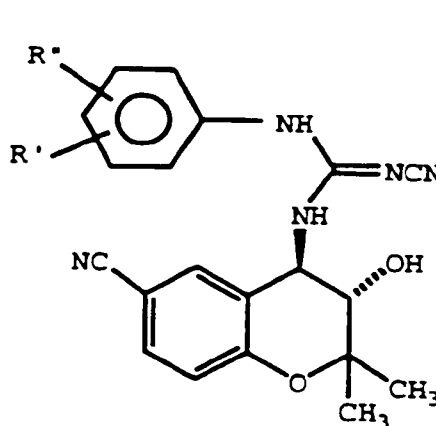
halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl (including phenyl substituted with R' and R'' as defined below), (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

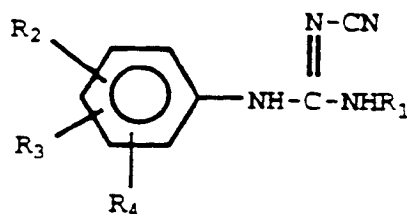
R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkyl; and n is 1, 2 or 3;

with the compound



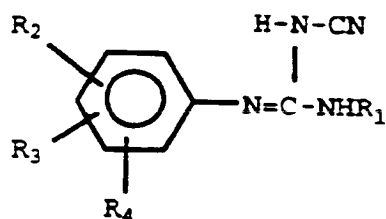
(where R' and R'' are independently hydrogen, cyano, alkyl, alkoxy, nitro, hydroxy, halo, haloalkyl, alkylthio, amino, -N(alkyl)₂, -NHalkyl or benzyloxy with the proviso that at least one of R' and R'' is other than hydrogen) being preferred;

D



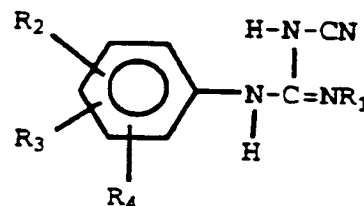
and its possible tautomers

D'

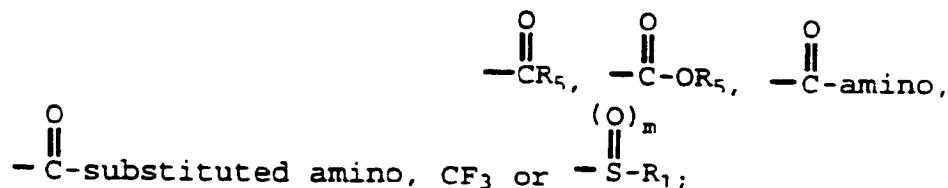


and

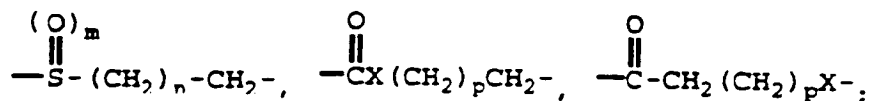
D''



wherein R₁ is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;
R₂ is -C≡N, -NO₂,



R₃ and R₄ are each independently selected from -R₂, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, -NHalkyl, -N-(alkyl)₂, -S-alkyl, -O-arylalkyl, -S-arylalkyl or -S-aryl, -O-aryl, -NHarylalkyl, or R₂ and R₃ taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from



wherein

m = 1 or 2;

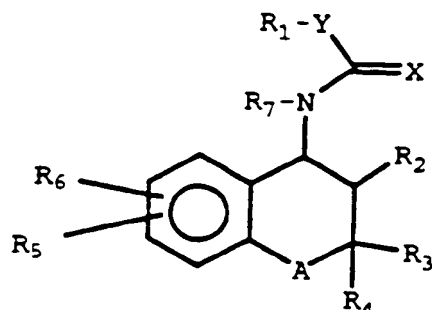
n = 1-3;

p = 0-2;

X is O, NR₅, CH₂; and,

R₅ is hydrogen or R₁;

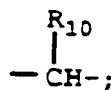
E



wherein A can be -CH₂-, -O-, -NR₉-, -S-, -SO- or -SO₂-, where R₉ is hydrogen or lower alkyl of 1 to 4 carbons;

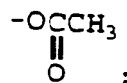
wherein X is oxygen or sulfur;

Y is -NR₈-, -O-, -S- or



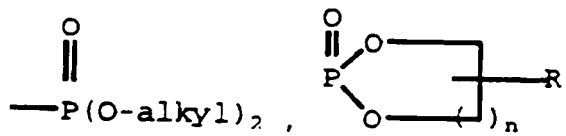
R₁ is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCCOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

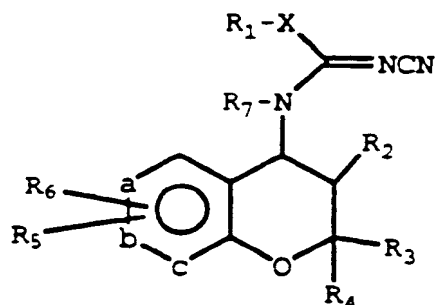
R₆ is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;

R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;

n is 1, 2 or 3; and,

R₁₀ is hydrogen, hydroxy, alkyl or O-alkyl;

E

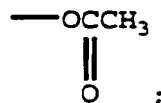


wherein a, b and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

where X is oxygen or sulfur;

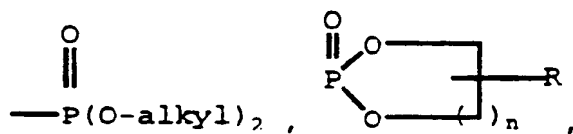
R₁ is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl;

R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,

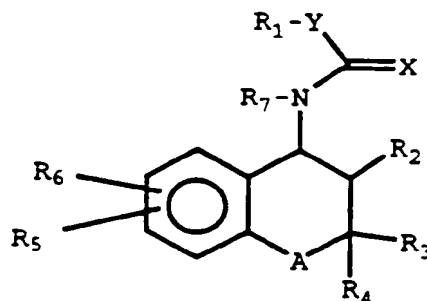


halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN and NO₂;

R₇ is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and, n is 1, 2 or 3; and,

G



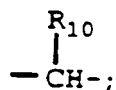
wherein A can be -CH₂-, -O-, -NR₃-, -S-, -SO- or -SO₂-, where R₃ is hydrogen or lower alkyl of 1 to 4

carbons;

wherein X is oxygen or sulfur;

Y is $-NR_8$, $-O-$, $-S-$ or

5

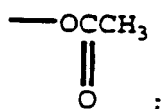


10

R₁ is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

R₂ is hydrogen, hydroxy,

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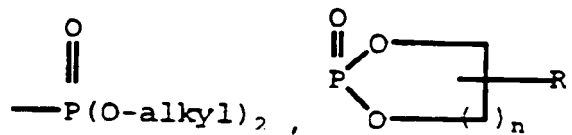


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R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,

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halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , $-\text{OCOalkyl}$, $-\text{OCONRalkyl}$, $-\text{NRCOalkyl}$ and NRCOOalkyl , NRCONR_2 wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl or haloalkyl;

R₆ is selected from H, alkyl, halo, OH, o-alkyl, amino and substituted amino, O-alkyl, OCOalkyl, OCONRalkyl, NRCOalkyl and NRCOOalkyl, NRCON(R)₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl or haloalkyl;

35

R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;

or R₁ and R₈, or R₁ and R₇, or R₇ and R₈ taken together can form a 5- to 7-membered saturated or unsaturated ring, which may further include an aryl group fused to 2 carbon atoms of such 5- to 7-membered ring;

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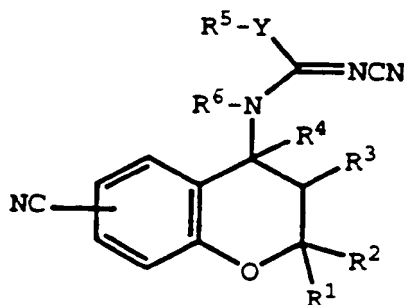
n is 1, 2 or 3; and,

R₁₀ is hydrogen, hydroxy, alkyl or O-alkyl.

45

H

50



55

wherein

R¹ and R² are each lower alkyl;

R^3 is hydroxy or acyloxy and R^4 is hydrogen or R^3 and R^4 are linked together to form a bond, and
 (i) Y is -S-, -O- or a group of the formula:



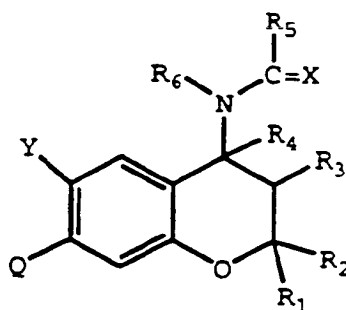
wherein R^7 is hydrogen, acyl or lower alkyl which may have suitable substituent(s), and

R^5 and R^6 are each hydrogen or lower alkyl.

(ii) Y is as defined above, and R^5 and R^6 are linked together to form lower alkylene, or

(iii) Y- R^5 is a heterocyclic group which may have suitable substituent(s), and R^6 is hydrogen or lower alkyl

I



and salts thereof, wherein

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-5} alkoxy or C_{1-7} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

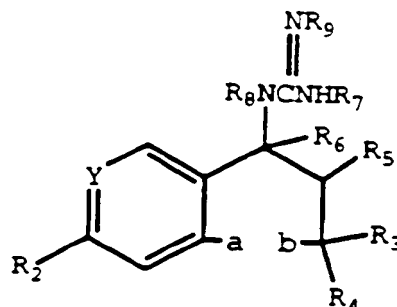
R_5 is hydrogen, C_{1-6} alkyl optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy or amino optionally substituted by one or two independent C_{1-6} alkyl groups, or C_{2-6} alkenyl, amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen, or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-12} carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups and R_6 is hydrogen or C_{1-6} alkyl, or R_5 and R_6 together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2 such that $m + n$ is 1 or 2 and Z is CH_2 , O, S or NR wherein R is hydrogen, C_{1-9} alkyl, C_{2-7} alkanoyl, phenyl C_{1-4} alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen; mono- or bi-cyclicheteroarylcarbonyl;

X is oxygen or sulphur;

Y and Q are electron withdrawing groups; and

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-5} alkoxy or C_{1-7} acyloxy;

K



wherein

a and b together form an -O- or -CH₂- linkage or a bond;
 either Y is N and R_2 is hydrogen; or
 Y is C-R₁;

wherein

either one of R_1 and R_2 is hydrogen and the other is nitro, cyano, halo, CF₃, formyl, aldoxime, CF₃O, NO₂-CH=CH-, NC-CH=CH-;

a group R_xX -wherein R_x is C₁₋₆alkyl, aryl or heteroaryl either of which may be optionally substituted by one, two or three of C₁₋₄alkyl, C₁₋₄alkoxy, nitro, halo, CF₃ and cyano; and X is C=O, O.C=O, C=O.O, CHOH, SO, SO₂, O.SO, O.SO₂, CONH, O.CONH, C=S, O.C=S, C=S.O, CH.SH, SONH, SO₂NH, O.SONH, O.SO₂NH, CO-CH=CH, C=NHOH, C=NNH₂;

or a group R_yR_zNZ - wherein R_y and R_z are independently hydrogen or C₁₋₆alkyl and Z is C=O, SO or SO₂; or

R_1 is a C₃₋₈cycloalkyl group or a C₁₋₆alkyl group optionally substituted by a group which is hydroxy, C₁₋₆alkoxy, amino optionally substituted by one or two C₁₋₆alkyl groups, C₁₋₇alkanoylino, C₃₋₈cycloalkyloxy or C₃₋₈cycloalkylamino; and R_2 is hydrogen; or

one of R_1 and R_2 is nitro, cyano or C₁₋₃alkylcarbonyl and the other is a different group selected from nitro cyano, halo, C₁₋₃alkylcarbonyl, methoxy or amino optionally substituted by one or two C₁₋₆alkyl or by C₂₋₇alkanoyl;

either one of R_3 and R_4 is hydrogen or C₁₋₄alkyl and the other is C₁₋₄alkyl; or

R_3 and R_4 together are C₂₋₅polymethylene;

either R_5 is hydrogen, hydroxy, C₁₋₆alkoxy or C₁₋₇acyloxy; and

R_6 is hydrogen; or

R_5 and R_6 together are a bond;

either R_7 is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆alkenyl or C₂₋₆alkynyl; and

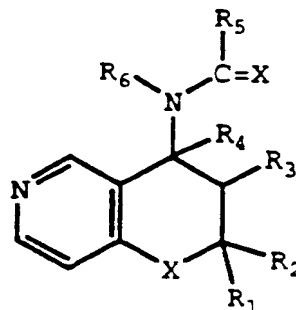
R_8 is hydrogen or C₁₋₆alkyl; or

R_7 and R_8 together are C₂₋₄polymethylene;

R_9 is CN, NO₂, COR₁₀ wherein R_{10} is C₁₋₃alkyl, NH₂, NH(C₁₋₃alkyl), CF₃ or phenyl optionally substituted as defined for R_x ; and

the $R_8N(NR_9)NHR_7$ moiety is trans to the R_5 group when R_5 is hydroxy, C₁₋₆alkoxy or C₁₋₇acyloxy;

L



wherein

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-6} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

R_5 is hydrogen; C_{1-6} alkyl optionally substituted by up to three halo atoms, by hydroxy, C_{1-4} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, or amino optionally substituted by one or two independent C_{1-6} alkyl groups or disubstituted by C_{4-5} polymethylene, C_{2-6} alkenyl; amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-2} carboxylic acyl or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; or (when X is O), R_5 is selected from the class of carboxy, C_{1-6} alkoxycarbonyl or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; and,

R_6 is hydrogen or C_{1-6} alkyl; or

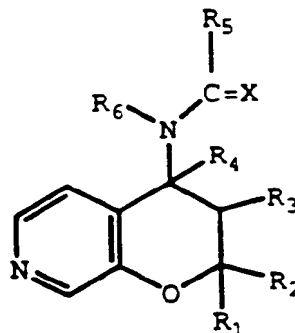
R_5 and R_6 together are $-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2 such that $m + n$ is 1 or 2 and Z is CH_2 , O, S or NR wherein R is hydrogen, C_{1-8} alkyl, C_{2-7} alkanoyl, phenyl, C_{1-4} alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen or R is heteroarylcarbonyl;

X is oxygen or sulphur; or

R_5 , R_6 , X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolinthione optionally substituted in the phenyl ring as defined for R above;

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-4} alkoxy or C_{1-7} acyloxy;

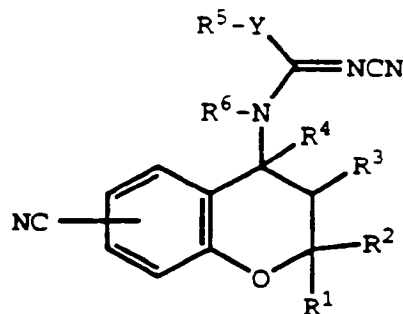
M



and pharmaceutically acceptable salts thereof, wherein R_1 is hydrogen or alkyl; R_2 is alkyl or R_1 and R_2 are polymethylene; R_3 is hydrogen, hydroxy, alkoxy, acyloxy; R_4 is hydrogen or R_3 and R_4 are a bond; R_5 is hydrogen, optionally substituted alkyl, alkenyl, optionally substituted amino, optionally substituted aryl or heteroaryl, carboxy, alkoxycarbonyl or aminocarbonyl; R_6 is hydrogen or alkyl or R_5

and R_6 together are $-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2, $m + n$ is 1 or 2, Z is CH_2 , O , S , NR , R is hydrogen, alkyl, alkanyl, phenyl-alkyl, naphthylcarbonyl, phenylcarbonyl, benzylcarbonyl, or heteroaryl-carbonyl; X is O , S or R_5 , R_6 , X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolin-thione;

N



wherein

- R^1 and R^2 are each lower alkyl;
- R^3 is hydroxy or acyloxy and R^4 is hydrogen; or
- R^3 and R^4 are linked together to form a bond, and
- (i) Y is $-S-$, $-O-$ or a group of the formula

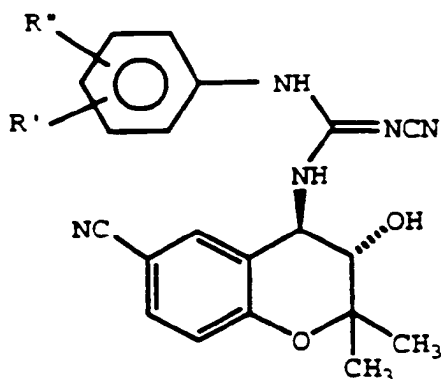


wherein

- R^7 is hydrogen, acyl or lower alkyl which may have suitable substituent(s); and
 - R^5 and R^6 are each hydrogen or lower alkyl;
 - (ii) Y is as defined above; and
 - R^5 and R^6 are linked together to form lower alkylene; or
 - (iii) $Y-R^5$ is a heterocyclic group which may have suitable substituent(s); and
 - R^6 is hydrogen or lower alkyl;
- and pharmaceutically acceptable salts thereof.

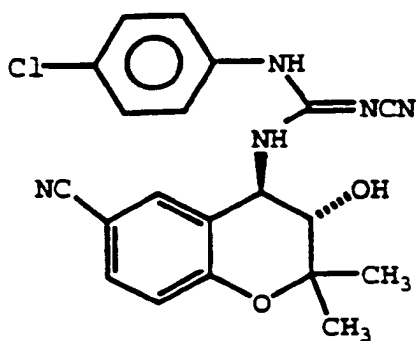
3. The use of claim 1 wherein the potassium channel activator has little or no vasorelaxant activity in normal tissue.
4. The use of claim 3 wherein said potassium channel activator is selected from C where R_7 is aryl, arylalkyl, heteroaryl and heteroaryl(alkyl), E, F or G where R_1 is aryl, arylalkyl, heteroaryl or heteroaryl(alkyl).
5. The use of claim 4 wherein the aryl group for R_7 in C or R_1 in E, F or G is substituted phenyl.
6. The use of claim 5 wherein the potassium channel activator is

C'



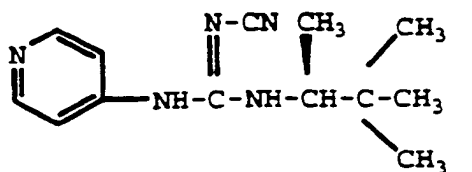
(where R' and R'' are independently hydrogen, cyano, alkyl, alkoxy, nitro, hydroxy, halo, haloalkyl, alkylthio, amino, -N(alkyl)₂, -NHalkyl or benzyloxy with the proviso that at least one of R' and R'' is other than hydrogen) being preferred;

7. The use of claim 6 wherein the potassium channel activator is



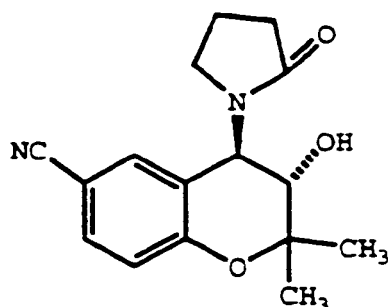
8. The use of claim 1 wherein said ulcerative condition of the gastrointestinal tract is induced by the administration of one or more antiinflammatory drugs.
9. The use of claim 8 wherein said medicament is for use concurrently with the antiinflammatory drug.
10. The use of claim 9 wherein said medicament and said antiinflammatory drug are provided by a single, combination dosage form.
11. Use of a potassium channel activator receptor antagonist for manufacturing a medicament for use concurrently with a therapeutically effective amount of an anti-inflammatory agent for preventing or treating an inflammatory condition without causing gastrointestinal ulcers, in a mammalian species.
12. The use of claim 11 wherein said potassium channel activator is nicorandil, minoxidil, a compound of the formula

A



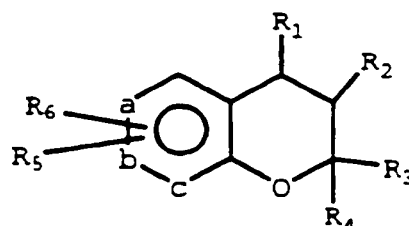
known as pinacidil;

B



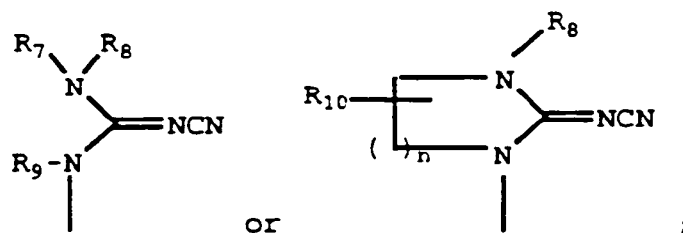
known as cromakalim;

C

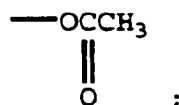


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R₁ is

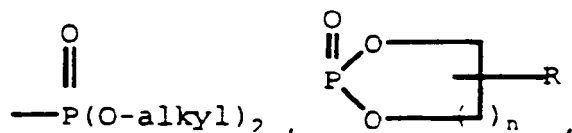


R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or, R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



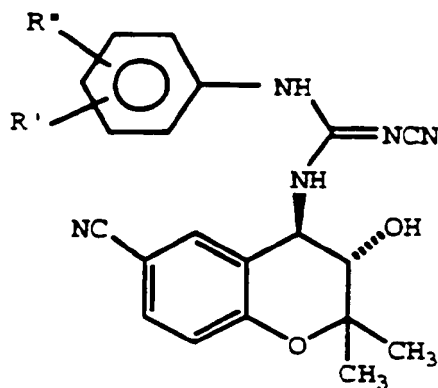
halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , $-\text{OCOalkyl}$, $-\text{OCONRalkyl}$, $-\text{NRCOalkyl}$ and NRCOOalkyl , NRCONR_2 wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO₂;

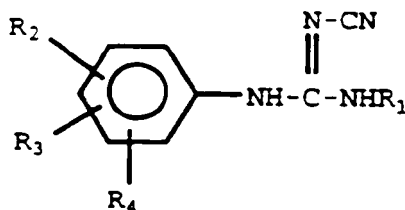
R₇ and R₈ are each independently selected from hydrogen, alkyl, alkenyl, aryl (including phenyl substituted with R' and R'' as defined below), (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R₇ and R₈ taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphiliny, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R₉ and R₁₀ are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkyl; and n is 1, 2 or 3;

with the compound

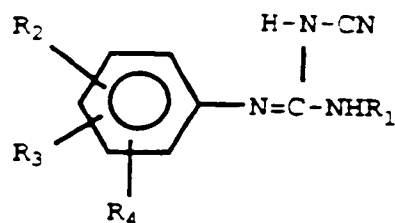


(where R' and R'' are independently hydrogen, cyano, alkyl, alkoxy, nitro, hydroxy, halo, haloalkyl, alkylthio, amino, -N(alkyl)₂, -NHalkyl or benzyloxy with the proviso that at least one of R' and R'' is other than hydrogen) being preferred;



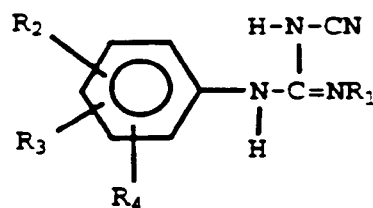
and its possible tautomers

D'

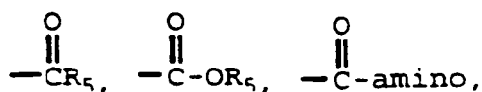


and

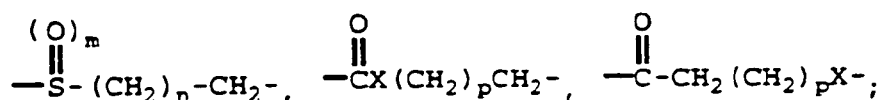
D''



wherein R_1 is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;
 R_2 is $-C\equiv N$, $-NO_2$.



R_3 and R_4 are each independently selected from $-R_2$, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, $-NH$ alkyl, $-N$ -(alkyl) $_2$, $-S$ -alkyl, $-O$ -arylalkyl, $-S$ -arylalkyl or $-S$ -aryl, $-O$ -aryl, $-NH$ arylalkyl, or R_2 and R_3 taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from



wherein

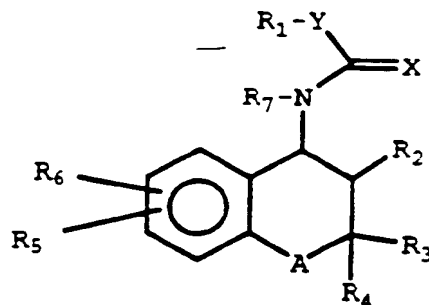
$m = 1$ or 2 ;

$n = 1-3$;

$p = 0-2$;

X is O , NR_5 , CH_2 ; and,

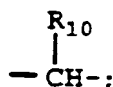
R_5 is hydrogen or R_1 ;

E

wherein A can be $-\text{CH}_2-$, $-\text{O}-$, $-\text{NR}_9-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{SO}_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;

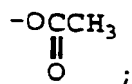
wherein X is oxygen or sulfur;

Y is $-\text{NR}_8$, $-\text{O}-$, $-\text{S}-$ or



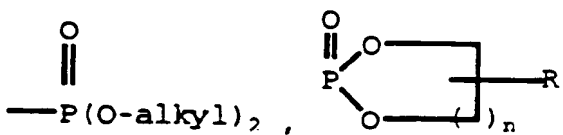
R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{COR}$, $-\text{COOR}$, $-\text{CONHR}$, $-\text{CONR}_2$, $-\text{CF}_3$, S-alkyl, $-\text{SOalkyl}$, $-\text{SO}_2\text{alkyl}$,



halogen, amino, substituted amino, O-alkyl, OCF_3 , OCH_2CF_3 , $-\text{OCOalkyl}$, $-\text{OCONRalkyl}$, $-\text{NRCOalkyl}$ and NRCCOalkyl , NRCONR_2 wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

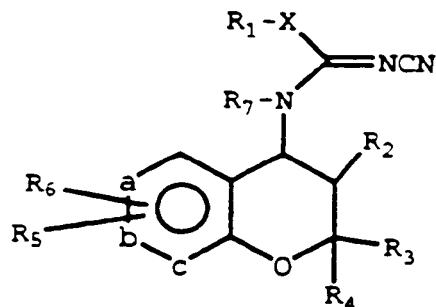
R_6 is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;

R_7 and R_8 are each independently selected from hydrogen, alkyl, arylalkyl;

n is 1, 2 or 3; and,

R_{10} is hydrogen, hydroxy, alkyl or O-alkyl;

F

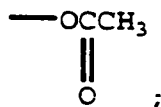


wherein a, b and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

where X is oxygen or sulfur;

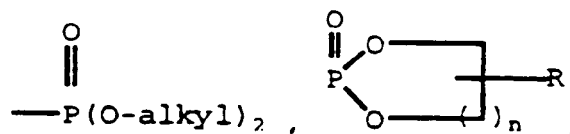
R₁ is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl;

R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or R₃ and R₄ taken together with the carbon atom to which they are attached form a 5-to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,

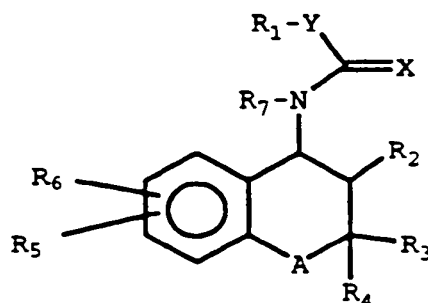


halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NR₂COalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R₆ is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN and NO₂;

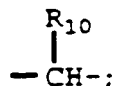
R₇ is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and, n is 1, 2 or 3; and,

G

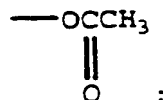


wherein A can be -CH₂-, -O-, -NR₉-, -S-, -SO- or -SO₂-, where R₉ is hydrogen or lower alkyl of 1 to 4 carbons;

wherein X is oxygen or sulfur;
Y is -NR₈, -O-, -S- or

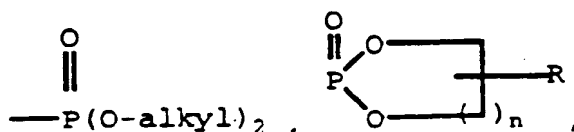


R₁ is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl.
R₂ is hydrogen, hydroxy,



R₃ and R₄ are each independently hydrogen, alkyl or arylalkyl, or R₃ and R₄ taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R₅ is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO₂, -COR, -COOR, -CONHR, -CONR₂, -CF₃, S-alkyl, -SOalkyl, -SO₂alkyl,



halogen, amino, substituted amino, O-alkyl, OCF₃, OCH₂CF₃, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCCOalkyl, NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl or haloalkyl;

R₆ is selected from H, alkyl, halo, OH, o-alkyl, amino and substituted amino, O-alkyl, OCOalkyl, OCONRalkyl, NRCCOalkyl and NRCONR₂ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl or haloalkyl;

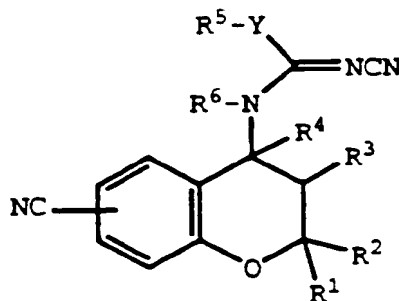
R₇ and R₈ are each independently selected from hydrogen, alkyl, arylalkyl;

or R₁ and R₈, or R₁ and R₇, or R₇ and R₈ taken together can form a 5- to 7-membered saturated or unsaturated ring, which may further include an aryl group fused to 2 carbon atoms of such 5- to 7-membered ring;

n is 1, 2 or 3; and,

R₁₀ is hydrogen, hydroxy, alkyl or O-alkyl.

H



wherein

R¹ and R² are each lower alkyl;

R³ is hydroxy or acyloxy and R⁴ is hydrogen or R³ and R⁴ are linked together to form a bond, and

(i) Y is -S-, -O- or a group of the formula:



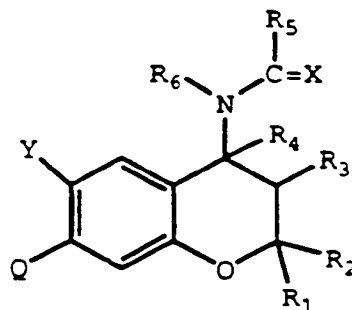
wherein R^7 is hydrogen, acyl or lower alkyl which may have suitable substituent(s), and

R^5 and R^6 are each hydrogen or lower alkyl,

(ii) Y is as defined above, and R^5 and R^6 are: linked together to form lower alkylene, or

(iii) Y- R^5 is a heterocyclic group which may have suitable substituent(s), and R^6 is hydrogen or lower alkyl

I



and salts thereof, wherein

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

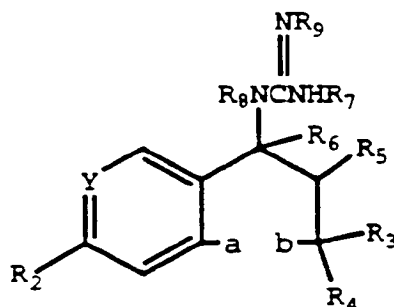
R_5 is hydrogen, C_{1-6} alkyl optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxy-carbonyl, carboxy or amino optionally substituted by one or two independent C_{1-6} alkyl groups, or C_{2-6} alkenyl, amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen, or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-12} carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups and R_6 is hydrogen or C_{1-6} alkyl, or R_5 and R_6 together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2 such that $m + n$ is 1 or 2 and Z is CH_2 , O, S or NR wherein R is hydrogen, C_{1-9} alkyl, C_{2-7} alkanoyl, phenyl C_{1-4} alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen; mono- or bi-cyclicheteroarylcarbonyl;

X is oxygen or sulphur;

Y and Q are electron withdrawing groups; and

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy;

K



wherein

a and b together form an -O- or -CH₂- linkage or a bond;
 either Y is N and R₂ is hydrogen; or
 Y is C-R₁;

wherein

either one of R₁ and R₂ is hydrogen and the other is nitro, cyano, halo, CF₃, formyl, aldoxime, CF₃O, NO₂-CH=CH-, NC-CH=CH-;

a group R_xX-wherein R_x is C₁₋₆alkyl, aryl or heteroaryl either of which may be optionally substituted by one, two or three of C₁₋₄alkyl, C₁₋₄alkoxy, nitro, halo, CF₃ and cyano; and X is C=O, O.C=O, C=O.O, CHOH, SO, SO₂, O.SO, O.SO₂, CONH, O.CONH, C=S, O.C=S, C=S.O, CH.SH, SONH, SO₂NH, O.SONH, O.SO₂NH, CO-CH=CH, C=NHOH, C=NNH₂;

or a group R_yR_zNZ- wherein R_y and R_z are independently hydrogen or C₁₋₆alkyl and Z is C=O, SO or SO₂; or

R₁ is a C₃₋₈acycloalkyl group or a C₁₋₆alkyl group optionally substituted by a group which is hydroxy, C₁₋₆alkoxy, amino optionally substituted by one or two C₁₋₆alkyl groups, C₁₋₇alkanoylino, C₃₋₈cycloalkyloxy or C₃₋₈cycloalkylamino; and R₂ is hydrogen; or

one of R₁ and R₂ is nitro, cyano or C₁₋₃alkylcarbonyl and the other is a different group selected from nitro cyano, halo, C₁₋₃alkylcarbonyl, methoxy or amino optionally substituted by one or two C₁₋₆alkyl or by C₂₋₇alkanoyl;

either one of R₃ and R₄ is hydrogen or C₁₋₄alkyl and the other is C₁₋₄alkyl; or

R₃ and R₄ together are C₂₋₅polymethylene;

either R₅ is hydrogen, hydroxy, C₁₋₆alkoxy or C₁₋₇acyloxy; and

R₆ is hydrogen; or

R₅ and R₆ together are a bond;

either R₇ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆alkenyl or C₂₋₆alkynyl; and

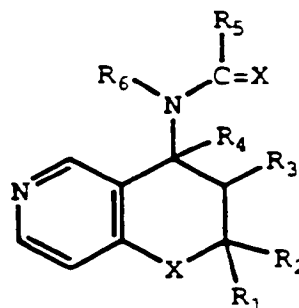
R₈ is hydrogen or C₁₋₆alkyl; or

R₇ and R₈ together are C₂₋₄polymethylene;

R₉ is CN, NO₂, COR₁₀ wherein R₁₀ is C₁₋₃alkyl, NH₂, NH(C₁₋₃alkyl), CF₃ or phenyl optionally substituted as defined for R_x; and

the R₈N(NR₉)NHR₇ moiety is trans to the R₅ group when R₅ is hydroxy, C₁₋₆alkoxy or C₁₋₇acyloxy;

L



wherein

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-6} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

R_5 is hydrogen; C_{1-6} alkyl optionally substituted by up to three halo atoms, by hydroxy, C_{1-4} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, or amino optionally substituted by one or two independent C_{1-6} alkyl groups or disubstituted by C_{4-5} polymethylene, C_{2-6} alkenyl; amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-12} carboxylic acyl or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; or (when X is O). R_5 is selected from the class of carboxy, C_{1-6} alkoxycarbonyl or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; and,

R_6 is hydrogen or C_{1-6} alkyl; or

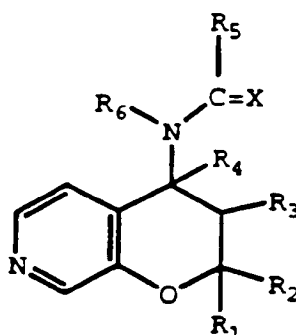
R_5 and R_6 together are $-\text{CH}_2-(\text{CH}_2)_n-\text{Z}-(\text{CH}_2)_m-$ wherein m and n are 0 to 2 such that $m + n$ is 1 or 2 and Z is CH_2 , O, S or NR wherein R is hydrogen, C_{1-8} alkyl, C_{2-7} alkanoyl, phenyl, C_{1-4} alkyl, naphthylcarbonyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen or R is heteroarylcarbonyl;

X is oxygen or sulphur; or

R_5 , R_6 , X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolinthione optionally substituted in the phenyl ring as defined for R above;

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-4} alkoxy or C_{1-7} acyloxy;

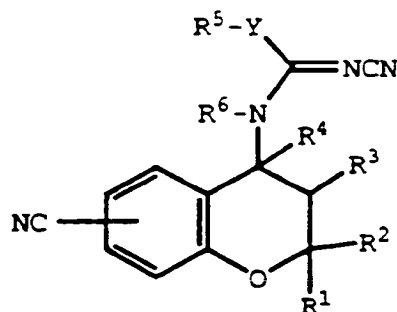
M



and pharmaceutically acceptable salts thereof, wherein R_1 is hydrogen or alkyl; R_2 is alkyl or R_1 and R_2 are polymethylene; R_3 is hydrogen, hydroxy, alkoxy, acyloxy; R_4 is hydrogen or R_3 and R_4 are a bond; R_5 is hydrogen, optionally substituted alkyl, alkenyl, optionally substituted amino, optionally

substituted aryl or heteroaryl, carboxy, alkoxycarbonyl or aminocarbonyl; R_5 is hydrogen or alkyl or R_5 and R_6 together are $-(CH_2)_n-Z-(CH_2)_m-$, wherein m and n are 0 to 2, $m + n$ is 1 or 2, Z is CH_2 , O, S, NR; R is hydrogen, alkyl, alkanoyl, phenyl-alkyl, naphthylcarbonyl, phenylcarbonyl, benzylcarbonyl, or heteroaryl-carbonyl, X is O, S or R_5 , R_5 , X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolin-thione.

N



wherein

- R^1 and R^2 are each lower alkyl;
- R^3 is hydroxy or acyloxy and R^4 is hydrogen; or
- R^3 and R^4 are linked together to form a bond, and
- (i) Y is $-S-$, $-O-$ or a group of the formula

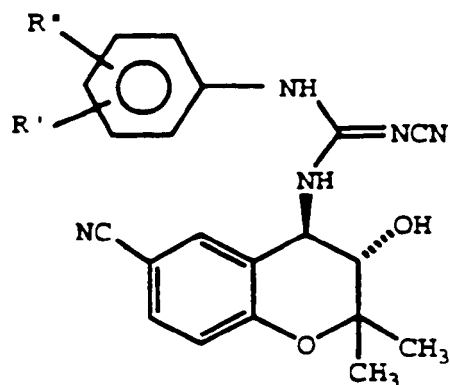


wherein

- R^7 is hydrogen, acyl or lower alkyl which may have suitable substituent(s); and
- R^5 and R^6 are each hydrogen or lower alkyl;
- (ii) Y is as defined above; and
- R^5 and R^6 are linked together to form lower alkylene; or
- (iii) $Y-R^5$ is a heterocyclic group which may have suitable substituent(s); and
- R^6 is hydrogen or lower alkyl;
- and pharmaceutically acceptable salts thereof.

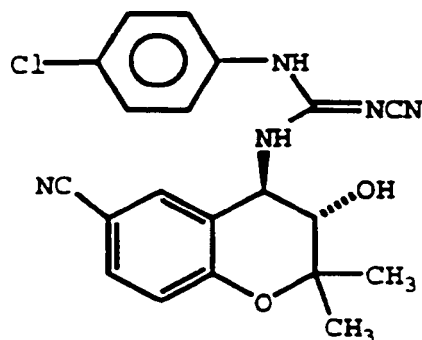
13. The use of claim 11 wherein the potassium channel activator has little or no vasorelaxant activity in normal tissue.
14. The use of claim 11 wherein said potassium channel activator is selected from C where R_7 is aryl, arylalkyl, heteroaryl and heteroaryl(alkyl), E, F or G where R_1 is aryl, arylalkyl, heteroaryl or heteroaryl(alkyl).
15. The use of claim 11 wherein the aryl group for R_7 in C or R_1 in E, F or G is substituted phenyl.
16. The use of claim 11 wherein the potassium channel activator is

p.

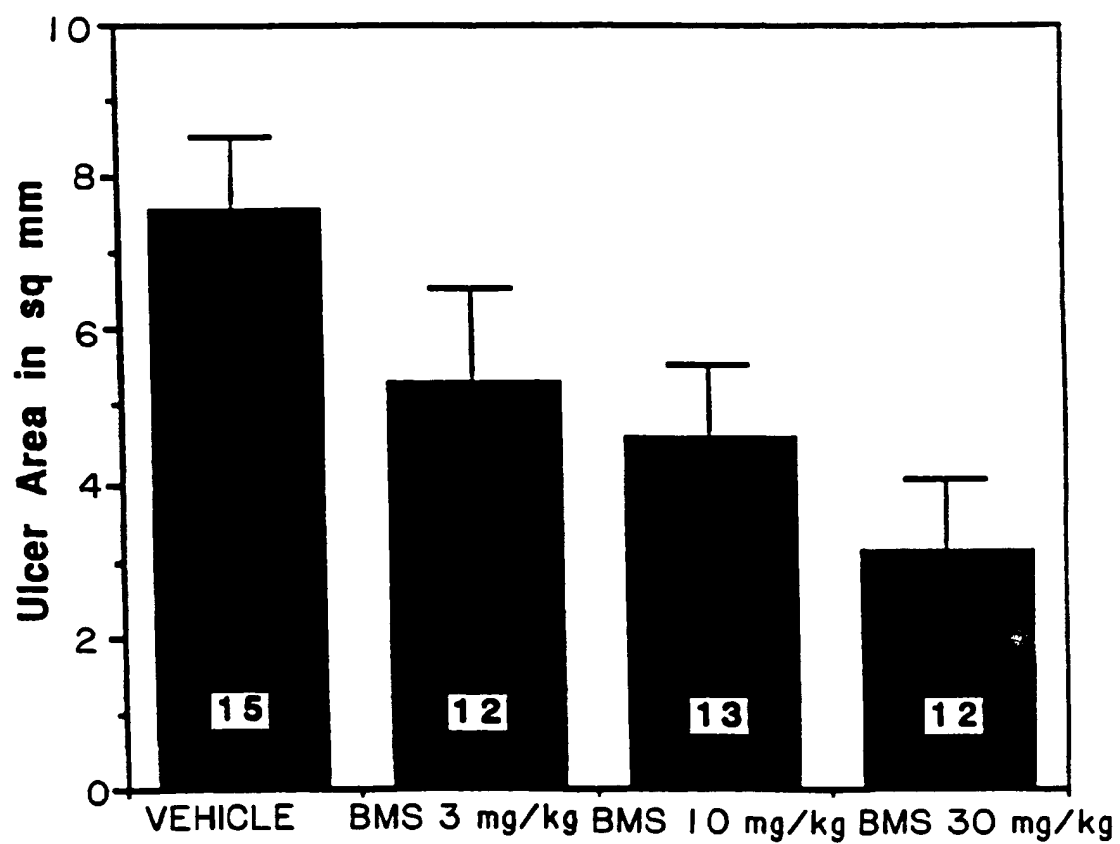


where R' and R'' are independently hydrogen, cyano, alkyl, alkoxy, nitro, hydroxy, halo, haloalkyl, alkylthio, amino, -N(alkyl)₂, -NHalkyl or benzyloxy with the proviso that at least one of R' and R'' is other than hydrogen.

17. The use of claim 11 wherein the potassium channel activator is



18. A pharmaceutical composition comprising an anti-ulcer amount of a potassium channel activator and an effective amount of an anti-inflammatory drug.



(19)



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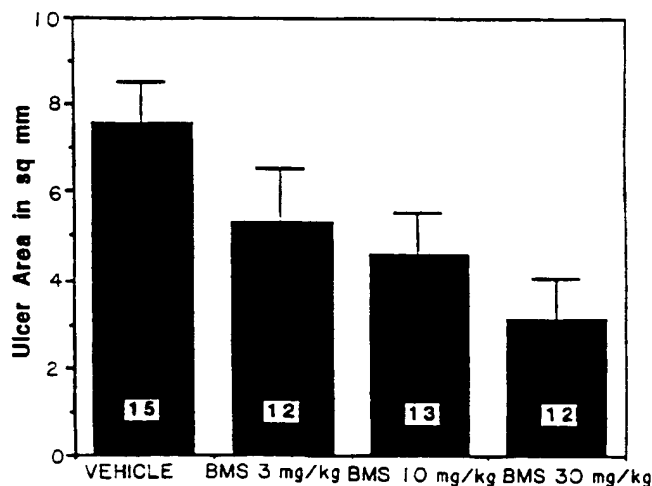
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(54) Use of potassium-channel activators for the manufacture of a medicament for the treatment of gastrointestinal ulcers

(57) Ulcerative conditions of the gastro-intestinal tract, e.g., antiinflammatory-drug-induced ulcers, are treated or prevented by the administration of a potassium channel activator. Methods and combination prod-

ucts are also disclosed for the treatment of inflammatory conditions without causing ulceration of the gastrointestinal tract.



EP 0 575 749 A3



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EUROPEAN SEARCH REPORT

Application Number
EP 93 10 8114

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claims	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	EP-A-0 389 861 (FUJISAWA PHARMACEUTICAL CO.; LTD.) * page 2, line 1-15 * * page 8, line 42 - line 44 * ---	1	A61K31/00 A61K31/35 A61K31/275 A61K31/38 A61K31/395 A61K31/435 A61K31/44
X	EP-A-0 432 893 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) * page 2, line 1 - line 5 * * page 16, line 1 - line 2 * ---	1	
D,X	EP-A-0 205 292 (BEECHAM GROUP PLC) * column 1, line 1 - column 2, line 7 * ---	1	
D,X	EP-A-0 274 821 (BEECHAM GROUP PLC) * page 3, line 12; claims 1-7 * ---	1	
D,X	EP-A-0 359 537 (BEECHAM GROUP PLC) * page 2, line 10 - line 16 * ---	1	
X	DATABASE WPI Week 9123 Derwent Publications Ltd., London, GB; AN 91-168378 XP002002053 & JP-A-03 101 621 (CHUGAI PHARMACEUTICAL KK) , 26 April 1991 * abstract * ---	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61K
Y	DATABASE WPI Section Ch, Week 9049 Derwent Publications Ltd., London, GB; Class B02, AN 90-363498 XP002002054 & HU-A-55 055 (SQUIBB & SONS INC E R) , 5 December 1990 * abstract * ---	1-8	
		-/--	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 3 May 1996	Examiner Tzschoppe, D
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>Δ : member of the same patent family, corresponding document</p>			

EPO FORM 1503 (03.92) (P04/001)



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EUROPEAN SEARCH REPORT

Application Number
EP 93 10 8114

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
D,P, Y	US-A-5 140 031 (KARNAIL ATWAL ET AL.) 18 August 1992 * column 1 - column 11 * -----	1-8	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 3 May 1996	Examiner Tzschoppe, D
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03 02 (P04C01)



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,

namely

see sheet -B-

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respects of which search fees have been paid, namely claims mentioned under items 1 and 5.
- ☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims



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EP 93 10 8114 -E-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.
Namely:

1. Claims 1-3 (partially) and 8 as far as nicorandil is concerned.
2. Claims 1-3 (partially) and 8 as far as minoxidil is concerned.
3. Claims 1-3 (partially) and 8 as far as pinacidil is concerned.
4. Claims 1-3 (partially) and 8 as far as cromakalim is concerned.
5. Claims 1-3 (partially) and 4-8 as far as the compounds of formula C are concerned.
6. Claims 1-3 (partially) and 8 as far as the compounds of formula D are concerned.
7. Claims 1-3 (partially) and 5,8 as far as the compounds of formula E are concerned.
8. Claims 1-3 (partially) and 5,8 as far as the compounds of formula F are concerned.
9. Claims 1-3 (partially) and 5,8 as far as the compounds of formula G are concerned.
10. Claims 1-3 (partially) and 8 as far as the compounds of formula H are concerned.
11. Claims 1-3 (partially) and 8 as far as the compounds of formula J are concerned.
12. Claims 1-3 (partially) and 8 as far as the compounds of formula K are concerned.
13. Claims 1-3 (partially) and 8 as far as the compounds of formula L are concerned.
14. Claims 1-3 (partially) and 8 as far as the compounds of formula M are concerned.
15. Claims 9-18

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EP 93 10 8114 -B2-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

The common concept linking the inventions nos. 1-15 seems to rely in the fact, that all the compounds are potassium channel activators and are effective in the treatment of the same diseases. As it is known from the documents listed in the search report that potassium channel activators are effective in the treatment of gastrointestinal disorders such as peptic ulcers or irritable bowel syndrome, this common concept is not novel.